Emergent Materials
https://doi.org/10.1007/s42247-020-00118-w

REVIEW

Carbonaceous nanomaterials for phototherapy: a review

Betül GÜRBÜZ[1] · Sümeyra AYAN[1] · Micheal BOZLAR[2] · Cem Bülent ÜSTÜNDAĞ[1]

Received: 19 February 2020 / Accepted: 7 August 2020

Abstract

Nowadays, cancer can be described as a common disease of our society. According to the World Health Organization, 8.2 million people in the world (approximately 0.11% of worldwide population) die each year from cancer. A major challenge for cancer therapy remains in developing cancer treatments with less toxicity. Conducted worldwide, over a period of 25 years, the outcomes of preclinical and clinical studies established phototherapy (PT) as a useful treatment for some cancer types. Photodynamic therapy (PDT) and photothermal therapy (PTT) are two critical PT treatments in order to damage tumor cells. PDT utilizes a combination of drugs, photosensitive molecules also known as photosensitizers (PSs), and visible light of an appropriate wavelength in order to activate drugs. PTT employs agents to generate heat from illumination. Most clinically confirmed PSs target superficial lesions because of their limited effects on cancerous tissues, and consequently, this approach causes non-effective therapy to deep-seated cancerous tissues. Combination of PDT and PTT with carbonaceous nanomaterials (CNs) offers additional active complementary and supplementary roles for deep tumors in cancer therapy. The effective delivery of therapeutic molecules into the cancer cell, containing surfaces, optimum sizes, and shapes of the CNs that are able to be enhanced with homing ligands and utilizable interactions. CNs have significant potential for biomedical applications, due to their unique well-designed size, composition, biocompatibility, and functionalities. CNs including graphene, graphene oxide (GO), carbon nanotubes (CNTs), and fullerenes (C_{60}) can act as efficient PS carriers for cancer treatment. Each material has advantages and disadvantages such as degradability, solubility, and drug loading capacity for cancer therapy. This review discusses the theranostic applications of CNs. Benefiting from other researches, CNs will be categorized with regard to their application and effectiveness in PT. The chemical modification of the mentioned substances before their biomedical applications will be briefly discussed. The advantages and limitations of these nanomaterials (NMs) provide a new perspective on improving cancer therapy using these CNs.

Keywords Carbonaceous nanomaterials · Cancer treatment · Phototherapy · Photodynamic therapy · Photothermal therapy

1 Introduction

Despite major progress achieved over the last decades, early diagnosis and efficient treatment of cancer remains exceedingly challenging. Common cancer treatments, such as surgery, radiotherapy, and chemotherapy, have the disadvantage and risk of damaging healthy cells and tissues [1]. In order to overcome such problems in cancer therapy, phototherapy (PT) opens new opportunities in various biological applications. PT is a form of light-based medical treatment [2], which has been used to treat various diseases such as neonatal hyperbilirubinemia [3] and cancer [4]. Photodynamic therapy (PDT) and photothermal therapy (PTT) are the two main types of PT [5] that have superior tissue penetration ability with near-infrared light (NIR), which is less toxic and can specifically target cancer cells under light irradiation without damaging normal tissues [6].

Heat treatment has been shown to be widely effective in limiting damages to biological tissues. Generally, higher temperatures accelerate tissue damages, with the likelihood of increasing exponentially above 43 °C [7]. PTT is expected to offer non-toxic and high tumor cell target ability to enhance therapeutic effect without causing any toxicity for normal

✉ Cem Bülent ÜSTÜNDAĞ
cbustun@yildiz.edu.tr; cbustundag@gmail.com

[1] Department of Bioengineering, Faculty of Chemical and Metallurgical Engineering, Yildiz Technical University, Esenler, 34210 Istanbul, Turkey

[2] School of Engineering and Applied Science, Department of Chemical and Biological Engineering, Andlinger Center of Energy and the Environment, Princeton University, Princeton, NJ 08544, USA

Published online: 13 August 2020

cells. Various carbonaceous nanomaterials (CNs) with NIR absorbance offer promising therapeutic efficiency in many real time in vivo examinations and in personalized treatment [8].

PDT is a safe and non-invasion procedure; it uses light-activated photosensitizers (PSs) that are able to produce active oxygen species (e.g., singlet oxygen ($^1O_2$), free radicals, and peroxides). PSs are able to irreversibly kill cancer cells. Photochemical reactions that occur between PSs and O_2 were produced by PDT and they depend on reactive oxygen species (ROS) [9]. Therapy commences with the injection of a proper amount of PSs into a patient's bloodstream. Then, the accumulation of PSs in tumor can be observed after an appropriate time interval [10]. PDT is generally used to treat actinic keratosis. It has been examined for the cure and prevention of skin cancers. Excellent cosmetic results, low invasiveness, and good tolerance are the advantages of topical PDT. However, a major disadvantage of PDT is pain [11]. The hypericin molecule, which is a type of PSs, is a natural photoactive pigment that is an effective photoreceptor [12]. This molecule is used as PSs in PDT, and is activated by visible light. It can be accumulated in tumors, matrices, and vessels, and it destroys the tumor via the production of ROS. This antitumor agent is found on *Hypericum perforatum* (also known as St. John's wort) [13]. Moreover, this pharmaceutical agent can be used to visualize tumor cells by its red fluorescent emission [14]. Another example of PSs is phthalocyanines. This molecule is less toxic and hydrophobic; therefore, it cannot be administered via intravenous routes. Phtalocyanines is activated by NIR at 600–850 nm wavelengths. Likewise hypericin and phthalocyanines can be accumulated in tumors, matrices, and vessels, and it destroys the tumor via the production of ROS [15]. Irradiation of light by using specific wavelength excites the PSs molecules. The absorption of energy by molecules causes transformation into an excited singlet state. Moreover, molecules can undergo the electron spin transformations for their triplet state. Formation of free radicals reacting with ground-state molecular oxygen (O_2) can lead to superoxide anion radicals, hydrogen peroxides, and hydroxyl radicals. The involvement of energy transfer in order to obtain chemically active $^1O_2$ is known as type two reaction. Both of these two pathways induce significant oxidative damage of cellular biomolecule, causing cell death [16] as shown in Fig. 1. The hypericin molecule is a natural photoactive pigment that is an effective photoreceptor [14]. This molecule is used as PSs in PDT, and is activated by visible light. It can be accumulated in tumors, matrices, and vessels, and it destroys the tumor via the production of ROS. This antitumor agent is found on *H. perforatum* (also known as St. John's wort) [15]. Moreover, this pharmaceutical agent can be used to visualize tumor cells by its red fluorescent emission [16].

PSs are the major factors in commanding the side effects and efficiency. Several unidentified complex mixtures of porphyrins constitute the first generation of PSs. However, poor selectivity in clinical applications, extended photosensitivity, and low light influence are the main limitations of porphyrins. Dealing with these problems, the second generation of PSs has been improved. In the 650–800 nm–wavelength range, two types of PSs are active producers of $^1O_2$ with strong absorption. Nevertheless, PSs are highly hydrophobic and they strongly aggregate in aqueous solution [17, 18]. Tailoring CNs in PDT has been an important task in solving challenges related to classic PSs. The effective deliveries of therapeutic molecules into tumor site, containing surfaces, are optimum sizes and shapes of the CNs that are able to be enhanced with homing ligands and utilizable interactions [19]. This statement illustrates that nanomaterials (NMs) have been widely used for cancer imaging and drug delivery systems (DDS). While materials combining with both diagnosis and therapy have been also known as a "theranostic," CNs can be used more actively for cancer theranostic applications. They possess strong absorption in NIR regions and supply beneficial PDT effect for CNs [19].

In the procedure of PDT, PSs transport photon energy to the environment, where O_2 generates ROS like $^1O_2$ in order to accomplish an effective cure under the irradiation of light [20]. The types of PSs that are produced $^1O_2$ often concentrate organic molecules such as dyes, porphyrins, phthalocyanines, and some macrocyclic systems. However, most of PSs examined are sensitive to light, which reduces the production efficiency of excited molecules [21]. Different aqueous-based organic matter samples manufacture $^1O_2$ with quantum yields of $^1O_2$ 0.59–4.5% at 365 nm [22]. The quantum yields of $^1O_2$ play a significant role on cancer diagnosis and PDT. Heavy atoms such as bromide and iodine can increase the quantum yield of $^1O_2$ [23]. However, clinical applications of PDT agents are frequently limited by their low $^1O_2$ quantum yields. Graphene-based PDT like quantum dots (QDs) constitute an alternative to current PDT agents, which have a quantum yield as low as ~ 1.3 [24].

PT based on CNs can be used as a delivery system in cancer therapy. CNs including graphene (two dimensional), carbon nanotubes (CNTs) (one dimensional), and fullerene (C_{60}) (dimensionless) have been advanced as nano delivery systems for drugs and utilized as photothermal agents for PDT due to their NIR optical absorbance [25]. The structural characteristics of different CNs are shown in Fig. 2.

Graphene structures are members of a wide family of graphitic NMs, with high surface area and as a single atom thick sheet. Due to the chemically active sites for drug molecules via multi aromatic surface, graphene is a good candidate for DDS. Other good candidates for PT are CNTs. CNTs allow non-invasive treatment, non-toxic, and highly effective therapeutic agents using NIR laser irradiation. The potential applications of C_{60} rapidly increased in recent years. It is generally composed of 60 carbon atoms organized in a soccer ball

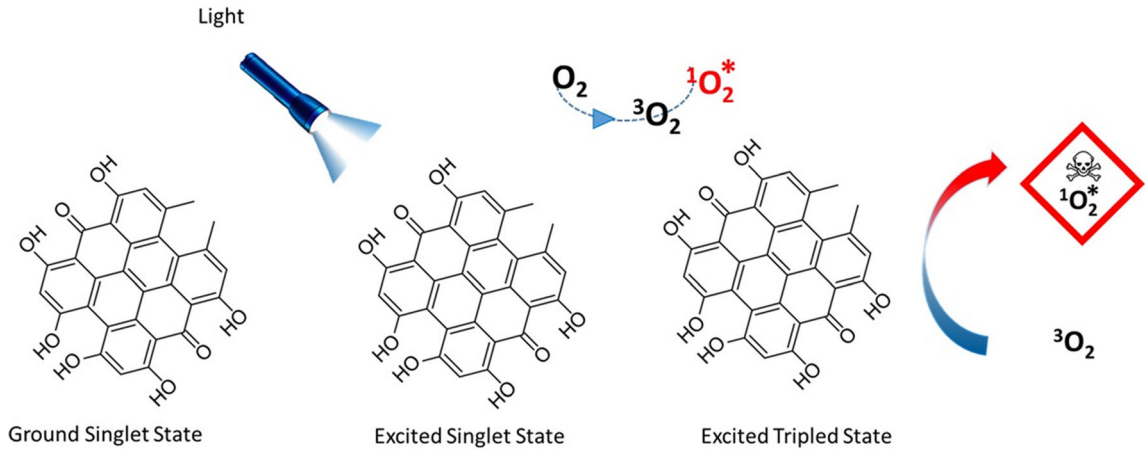

Fig. 1 Schematic PDT mechanisms for hypericin is an example of a PS

structure. Readily available aromatic rings in C_{60} lead to spreading π-conjugated systems of molecular orbitals and thereby to important absorption of visible light. C_{60} can generate ROS upon illumination, which supports their potential in PT [26, 27].

CNs offer considerable advantages such as hydrophilicity and suitable sizes for utmost tumor uptake via enhanced permeability and retention (EPR) effect. In order to improve tumor selection and decrease side effects, a proper design of these NMs can enable the transport of active agents and targeting groups [28]. In recent years, due to these reasons, CNs in PT have been intensely investigated as possible therapy methods to multiple cancer forms.

In this review, we focus on the benefits of improvements in PT for cancer therapy like PTT and PDT with the combination of CNs. Comparison between conventional techniques used in the treatment of cancer, such as chemotherapy, radiotherapy, and PT are examined. Our investigations indicate that PDT and PTT show decreased side effects and better selectivity compared to traditional methodologies. Moreover, different kinds of nano-agents for carrying out PTT and PDT, as well as using both of them are also reviewed in this review paper.

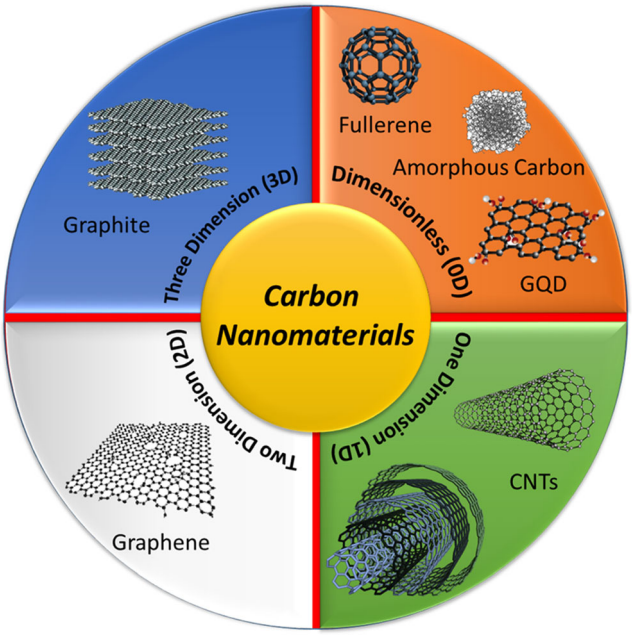

Fig. 2 The schematic illustration of the CNs family

2 Phototherapy for cancer treatment

For most cancer types, surgical resection is utilized as a widespread therapeutic method. But the many drawbacks of this method require the development of alternative cancer therapies such as chemotherapy, radiotherapy, or a combination of both of them. These therapies reduce pain and postsurgical complications and also speed recovery, but are still not completely free of side effects. They can cause hair loss, mouth sores, and skin redness, and, most importantly, destroy or slow down the growth of normal cells. To improve patient care, non-invasive PTT and PDT have become preferred cancer treatments [29].

PDT offers an alternative tumor-ablative and function in cancer therapy. It was initially explored in the early 1900s. In 1975, Dougherty et al. [30] used hematoporphyrin derivatives (HPD) that exhibited tumor localization and phototoxicity properties to demonstrate HPDs' success as PSs in PDT. But, the administration of tumor-localizing photosensitizer with light of a particular wavelength turns inactive molecules into cytotoxic compounds. Therapeutic effects occurred after light-induced processes triggered apoptosis or necrosis in the tumor by spurring an immune response against tumor cells that damaged tumor vasculature and cut the supply of O_2 and nutrients to the cancer cells. This mechanism of PT is illustrated in Fig. 3. It has since been shown that direct tumor destruction, antitumor immune response, and tumor vasculature shutdown are significant cell death mechanisms for PDT [31]. A combination of multiple PDT mechanisms may cause

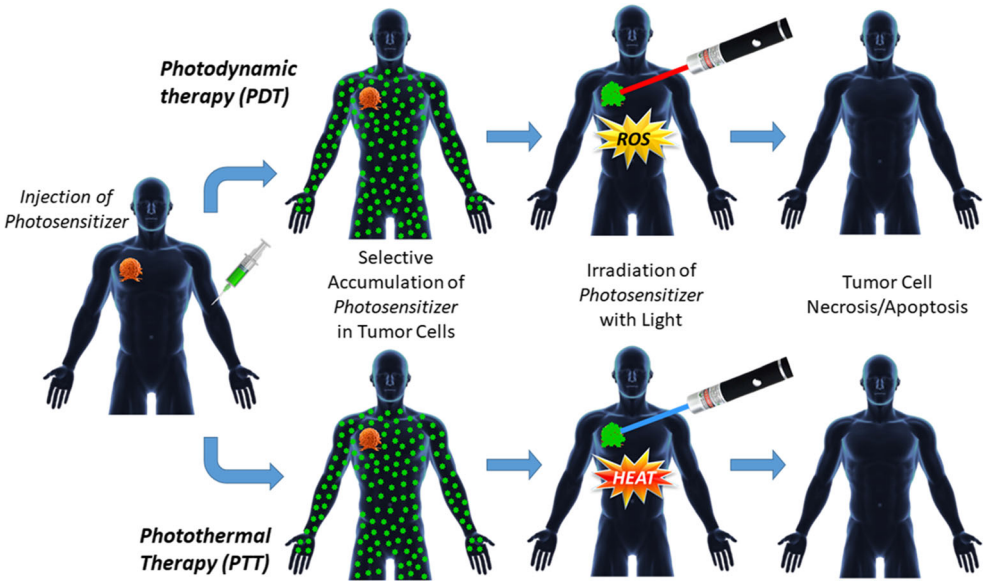

Fig. 3 Schematic representation of PT in cancer treatment

long-term tumor control via antitumor action against both the primary and metastatic tumors. Available research has depicted PDT as a promising treatment for early-stage cancer patients. Patients with intraperitoneal tumors, breast cancer, intraocular tumors, brain tumors, cholangiocarcinoma, head and neck tumors, colorectal cancer, gynecological tumors, cutaneous malignancies, mesothelioma, and pancreatic cancers have been treated with PDT [32].

NMs, which have diameters about 100 nm, are used in various applications because of their tunable physical, chemical, and biological properties with enhanced performance over their bulk counterparts [33]. Manufactured gold nanoparticles (AuNPs) are able to absorb light at specific wavelengths and activated via NIR, passively distribute the material through the body, where it is able to localize in tumors and be safely excreted so that it is used for neither cancer treatments nor medical imaging applications [34]. Yu et al. [35] proposed a productive cancer therapeutic system, shown in Fig. 4. They prepared biocompatible chitosan nanofibers (CNfs) installed into a pH-responsive motif, where the material is able to deliver bidirectional and activatable materials for a decrease of the tumor volume. Nanosized CNfs are active during cell interaction and steady in blood circulation. Because of their amine group, CNfs can bind with a large number of photothermal AuNPs and photodynamic chlorin e6 (Ce6). Cationic CNfs are an innovative approach to efficiently deplete AuNPs near tumors. This complex is bound to the pH-sensitive motif by electrostatic repulsion and specifically binds to tumor cells. The nature of the electrical charge of tumor cells is usually anionic. Therefore, due to electrostatic effect, the complexes prepared by Yu and co-workers can bind to target tumor cells. Their study demonstrated that via these actions, endocytosed Ce6 (on CNf) and AuNPs (independent from CNf) importantly responded to tumor cell death under light irradiation. To sum up their examination, the synergistic interaction of thermogenesis and photodynamic action led to a decrease in tumor development and growth increase upon exposure to light.

3 CNs in medicine

Many types of research claim that the aforementioned advantages of CNs as a diagnosis and DDS may lead to a target of personalized cancer therapy. By through neither hydrophobic interaction nor π-π stacking, many drugs molecules can be easily absorbed on their surface. After assemblies of drugs with carbonaceous, NMs can accumulate in the tumor region by active targeting or the EPR effect [36]. Thanks to distinct pharmacokinetic behavior of CNs, they can not only destroy tumor cells but also reduce the toxicity of the surrounding healthy tissues. When a suitable functionalization strategy is applied, CNs demonstrate effectiveness for cancer theranostic applications [37].

Common properties such as adjustable functional groups on the surface of CNs make them susceptible to functionalization against biological effects such as endothelial leakage [38]. CNs can also be used to build three-dimensional structures in medical applications as nanoscaffolds, biological detection, gene delivery, stem cell therapy (including stem cell proliferation), DDS, thermal therapy and imaging, and nanocomposites [27, 39].

Risk assessment of NMs provides an opportunity to apply modern concepts that are development for the common risk assessment of materials [40]. CNs reveal various biological responses (degradability) with respect to their shape, as seen from a comparison of Haniu and co-worker's examination [41].

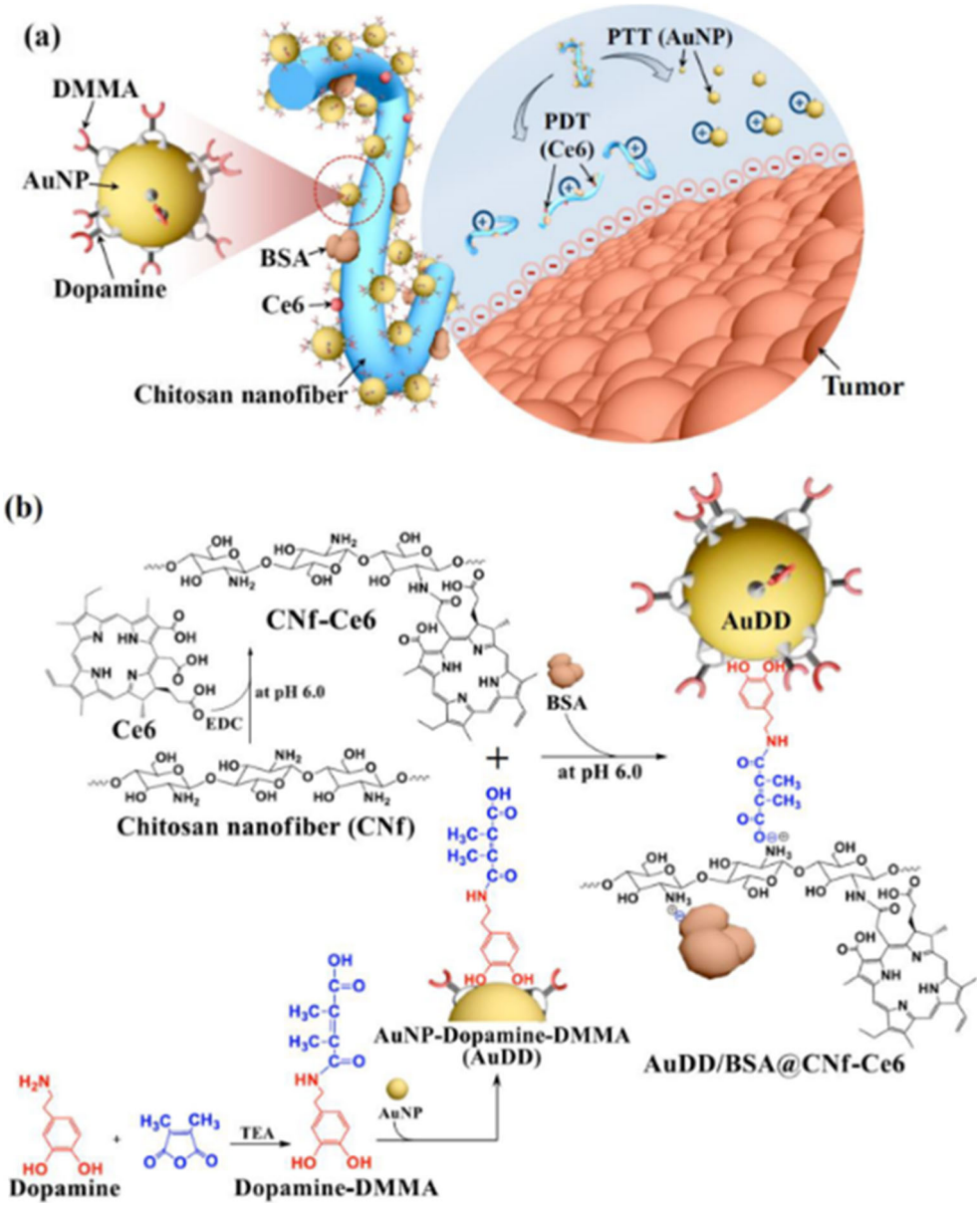

Fig. 4 Schematic illustration of Yu and co-workers' study: **a** for the integration of pH-sensitive chitosan nanofiber with AuNP, Ce6, and BSA; **b** for the synthesis of AuDD/BSA@CNf-AuDD-Ce6 [35]

3.1 Graphene in medicine

Graphene is a type of carbonaceous material that has the form of a perfectly flat sheet with sp^2 carbon atoms. The reduction of graphene oxide (GO) aims at manufacturing graphene-like materials with relatively structured and unique properties similar to graphene prepared directly from graphite [42]. Twisted bilayer graphene, which is resulting from two different monolayer graphene, can be considered as simple van der Waals heterostructures [43]. Nowadays, graphene-based medicine provides natural perspectives for diagnosis and treatment of future diseases. Potentially, graphene NMs used to synthesize prosthetic nerves, repairing destroyed nerve tissues and in nerve regeneration especially in spinal cord injuries, stem cell proliferation, gene delivery, and anticancer therapy. Mostly, functionalized graphenes are used for chemotherapy DDS [44]. The biomedical applications of graphene are illustrated in Fig. 5. In this therapy system, GO is loaded with specific PSs through π-π stacking and hydrophobic interactions [45].

QDs are a new perspective in order to target specific treatment regions. Newly graphene quantum dots (GQDs) are obtained from their larger two dimensional and which have superior properties such as high solubility and production of a high amount of singlet oxygen. This unique type of GQDs has a larger surface/volume ratio so that many cells can bind to QDs. Moreover, GQDs can be easily functionalized and they also have higher adjustability in physicochemical properties and fluorescence. However, the structure of QDs has some limitations; therefore, the synthesis strategy must be chosen correctly in order to improve their properties and applications.

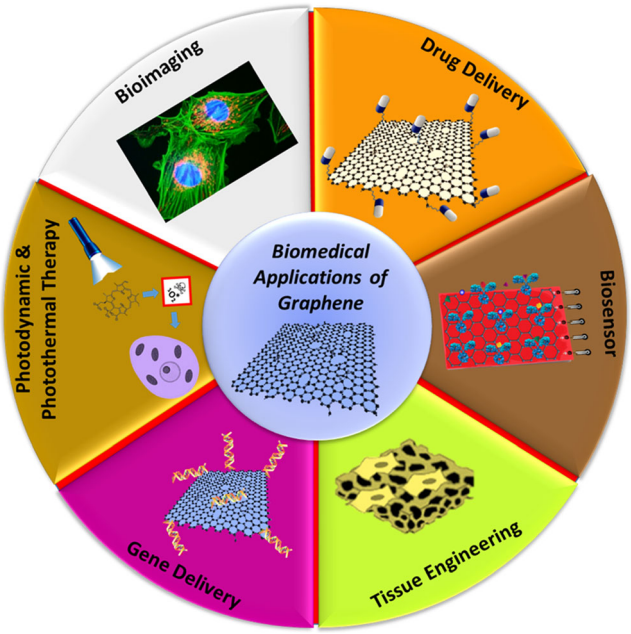

Fig. 5 Illustration of biomedical applications of graphene

Production parameters of QDs are effective on their sizes, defect degrees, edge configurations, chemical modifications, and thicknesses [46].

Xu et al. [47] have developed a therapy in combination with different therapeutic agents based on NMs for cancer treatment. In their study, an anticancer nanocomposite was manufactured by assembling a photothermal agent (copper sulfide nanoparticles, CuSNPs) and a photodynamic agent (g-C_3N_4 QDs) (graphitic-phase carbon nitride) on up-conversion nanoparticles (UCNPs). The surface modification of nanocomposites (CUSCs) was obtained with modification of polyethylene glycol (PEG) and folic acid (FA). The ultimate sample is produced as CUSCs-PEG-FA as a perfect cancer cell target and biocompatible system. In their manufactured nanoplatform by Xu and co-workers, CuSNPs are inorganic materials with a low-side effect on normal cells and high PTT. g-C_3N_4 QDs have perfect biocompatibility and are useful for cellular uptake because of their small sizes. UCNPs can be excited by NIR light (808 nm) in order to manufacture ultraviolet light emission. The combination of PTT and PDT can inhibit cancer compared to any monotherapy.

Martin et al. [48] designed DDS to target cells and showed an enhanced risk for biodegradation. The chemotactic peptide N-formyl-methionyl-leucyl-phenylalanine (fMLP) was used for functionalization of GO in their examination. fMLP interacts with the formyl peptide receptor that is expressed in various types of tumor tissues. GO is combined with fMLP in order to target and kill cancer cells and to obtain degradation capacity of the hybrid system. Biodegradation is adjusted using Raman spectroscopy and TEM. Their results illustrate that the hybrid system of GO-fMLP is susceptible to increase myeloperoxidase-mediated degradation. In their examination, HeLa cells are used for demonstration of GO-fMLP can deliver the chemotherapeutic agent (doxorubicin, DOX), containing higher levels of apoptosis. According to Martin and co-workers, GO-fMLP is a promising carrier that can adequately deliver anticancer drugs.

3.2 Carbon nanotubes in medicine

Nowadays, CNs are of great interest for different applications due to their low cytotoxicity, biocompatibility, inert, and ease of functionalization [49, 50]. In the past few years, the biomedical applications of CNTs have rapidly progressed and have become highly popular in the fields of targeted DDS, nanoscaffolding for tissue engineering, biomedical imaging, health monitoring, and disease detection for treatment [51]. CNTs have great potential for drug loading on the internal side of CNTs through the development of nanobottles to carry drugs in the organisms due to their penetration of cells without a particular cytotoxic effect [38, 51]. Therefore, CNTs that have the ability to target cancer cells can be explored for therapeutic delivery in vitro and in vivo [51]. Tumor specific therapeutic examinations are safe and effective perspectives in order to treat cancer. Management of nano vaccinology in order to condense the cancer vaccine potency might get over the requirement for the practice of neither high vaccine doses nor additional adjuvants. CNTs are able to enter different types of cells via diversified mechanisms using neither energy-dependent nor passive ways of cell uptake [52].

The physicochemical characteristics of CNTs play an important role in toxicity, pharmacokinetics, and metabolism of CNTs. Effectively functionalized CNTs either non-covalent or covalent methods can be used for biomedical applications [53]. The construction and shape of CNTs supply a unique benefit toward applications in regenerative medicine to improve stem cell production [38]. Despite their advantages, CNTs have some limitations due to their semiconductive nature; therefore, they cannot be used directly in clinical applications. Moreover, the variations in both size and length of CNTs require further chemical modification [39]. Another important limitation is the toxicity of CNTs [53, 54]. When CNTs are distributed in peripheral nervous system, lymphatic, and blood circulation, they can cause a toxic effect (leading to damages to the DNA) [39].

When different kinds of cells are cultured with CNTs, cytokine production, cytotoxicity, and oxidative stress occur [41]. Pulmonary exposure to CNTs results in the development of inflammation, fibrosis, and granulation in the lungs of rats and mice [55]. Biological responses to CNTs are influenced by multiple properties such as length, aspect ratio, fibrous surface area, shape (single wall or multi wall), and aggregation [41].

3.3 Fullerenes in medicine

C_{60} as an original kind of carbon allotropes has been examined for their distinctive properties and biological applications and in medicine. C_{60} structures are defined as symmetric cages of all sp^2 carbons that belong to neither five-membered nor six-membered rings on the cage surface. The space in a C_{60} cage is useful for encapsulating medically relevant materials like magnetic metals in order to diagnose and treat cancer cells. C_{60} has poor solubility in widely used organic solvents [56].

Recent developments proposed that C_{60}-based systems can open a new perspective in various areas such as in medical fields, C_{60} has some utilizable properties like appealing photo, electrochemical, and physical properties. C_{60} is also used as a radical scavenger and antioxidant. Moreover, when exposed to light, C_{60} can produce $^1O_2$ in high quantum yields. In addition to all these functions, C_{60} can be used for the delivery system of gene and drug [57].

3.4 Carbon dots

Carbon dots (Ca-Ds), also known as carbogenic dots, are a kind of spherical nanoparticles that have < 10-nm diameter size [24, 58]. Ca-Ds were found by Scrivens in 2004 during the purification of SWCNTs manufactured by an arc-discharge technique [59]. Ca-Ds are similar to QDs with metal due to their biocompatibility and combination. Ca-Ds are widely used materials as drug carriers, biosensors, bioimaging probes, and gene transmission [60]. The advantages of Ca-Ds are solubility; good photostability; easy modification; low toxicity; and excellent biocompatibility [61], intense multicolored photoluminescence, and minimal photobleaching [62]. On the other side, the high cost of Ca-Ds synthesis is a major disadvantage [61]. Their long-term metabolic fate in biological surroundings needs to be ascertained for in vivo examinations, for neither research nor clinical treat [62]. The average fluorescence lifetime of Ca-Ds is 6.46 ns [58].

Ca-Ds can be manufactured using various techniques such as plasma treatment, combustion/heating, electrochemical synthesis, laser ablation, supported routes, acidic oxidation, arc discharge, microwave/ultrasonic, and hydrothermal [59]. The surface modification of Ca-Ds with using functional groups (amino, hydroxy, and carboxyl groups) can strongly affect their properties. This modification can occur via either covalent modification (via silylation, amide coupling reactions, copolymerization, esterification, and sulfonylation) or non-covalent modification (via complexation/chelation, electrostatic interactions, and π-π interactions). Thus, the surface modification of Ca-Ds enables their use for DDS [63]. The degradation rate of Ca-Ds is interrelated with their surface chemistry and modification [62].

Wang et al. [64] manufactured highly dispersed, stable, and water-soluble photoluminescent Ca-Ds. In their study, they examined the toxicity of Ca-Ds. According to their results, Ca-Ds with various doses have not shown significant toxic effect on rats and mice. Moreover, Ca-Ds did not show any gene toxicity. Therefore, the manufactured Ca-Ds have good biocompatibility and potential use in vivo for both molecular imaging and biolabeling.

4 PT of graphene

The structure of graphene has been an attractive subject of debate over the years. Since 2004, studies of the applications of graphene have focused on many different fields, containing biomedicine, nanoelectronics, energy research, composite materials, and catalysis [65].

Graphene can be characterized as a two-dimensional, honeycomb-like network of flat, six-carbon rings molecules. A high external surface area provides the availability of aromatic drug molecules loading via π-π stacking [66], ballistic transport capacity, easy modification, mechanical strength, planar support for biomaterials, chemical inertness, high thermal conductivity, and optical transmittance that are exceptional properties of graphene [67]. Thanks to the unique interaction of graphene with biomolecules (e.g., nucleic acids), it can be used in clinical applications [38]. The unique physical and chemical properties of graphene combined with NIR absorbance make it as a new agent in PT in cancer [66]. The structure of a CNT can be seen as a single, rounded sheet of graphene. Various ways in which the graphene layer can be rolled up as illustrated in Fig. 6. Different imaginary cut lines show different CNT types with different properties.

4.1 Generation of singlet oxygen by graphene quantum dots

While PS molecules display a significant preference toward cancer cells, a lack of selective delivery of the molecules leads to high intake in non-cancer cells, which can cause considerable skin photosensitivity. To overcome this issue, QDs have been used in PDT [69]. Ca-Ds and GQDs are similar quantum-confined fluorescent carbonaceous materials and their spatial configurations, as well as their physical and chemical properties are the same. However, GQDs have high crystallinity unlike Ca-Ds [59]. Recent studies showed that QDs are excellent substances for charge and energy transfer processes that are probe transformation of stable molecules into cytotoxic materials in PDT. In order to exhibit cytotoxicity effect of GQDs, Markovic et al. [69] use U251 human glioblastoma cells as an in vitro as a model system to confirm ability of GQDs to generate $^1O_2$. Treatment with GQDs or blue light alone is not effective on the cell viability but

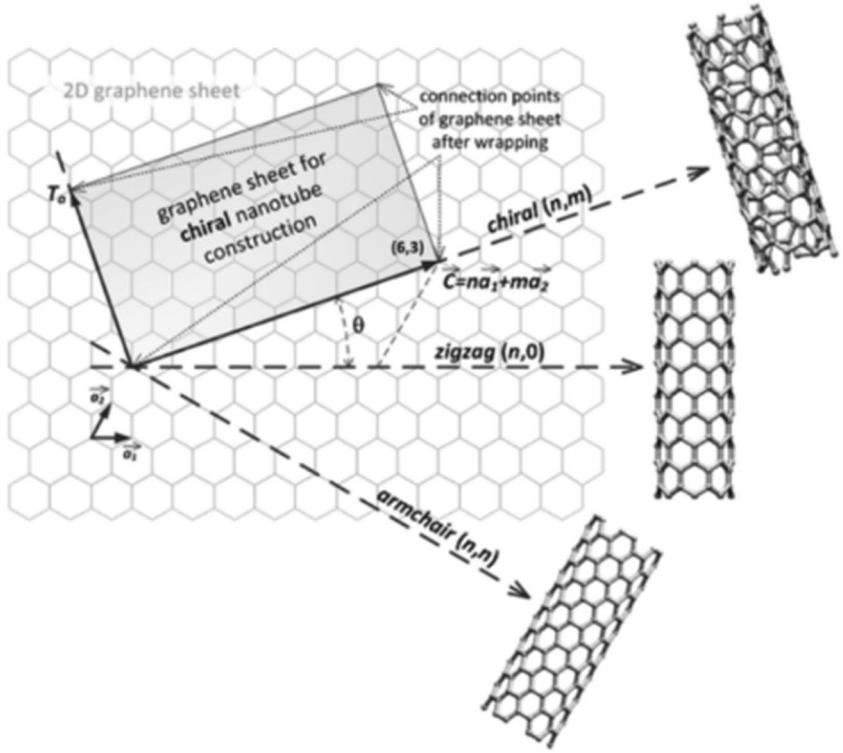

Fig. 6 The creation of a carbon nanotube from a single layer of graphene [68]

treatment with GQDs and blue light (470 nm) generate $^1O_2$ and causes cell death. In another study, via multistate sensitization process GQDs exhibited a high $^1O_2$ generation yield greater than 1.3 in the visible light region. Recent studies claim that in vitro and in vivo examinations are able to be used as PDT agents, and have been approved as highly efficient cancer treatment [70]. Over the past few years, GQDs were developed for use in deep-tissue imaging. However, due to their severe toxicity, QDs are far from approval for clinical trials. With respect to previous studies, gamma irradiation demonstrates great potential for the modification of graphene. Jovanovic et al. [71] applied gamma irradiation on graphene to enhance the photoluminescence properties. The significant outcome when the GQDs irradiated photoluminescence quantum yield reached six times higher than pristine ones. These results demonstrated that gamma irradiation directly impacts GQD ability to produce $^1O_2$. This makes low-dose irradiated GQDs promising candidates for PDT $^1O_2$. However, QDs-based PTT/PDT systems have some limitations such as constrain by the inherent tissue penetration depth of neither visible nor NIR light [46].

In order to determine the bio-safety of GQDs, Liu et al. [72] examined their effects on the embryonic development of zebrafish. Zebrafish embryos were exposed to GQDs, and then their mortality was examined. They determined that the mortality is increased while zebrafish's hatchability, heart rate, and spontaneous movement decreased with respect to concentration difference of GQDs. According to their study, GQDs meet environmental quality standards in order to protect human health.

4.2 Dual modality of graphene in cancer theranostic

Dual modality offers new opportunities to address the ever-increasing need for improvements in cancer therapy. Many strategies have been developed to use the advanced water solubility of graphene to establish a dual-modality nanoplatform for treatments, but this involves obstacles such as the chemical oxidation and loading of PS molecules. Bypassing the need for chemical oxidation and instead of achieving true dual modality of graphene would be an important improvement in cancer treatment [73].

Jiang et al. [74] present a water-soluble dual-modality therapy system graphene phthalocyanine–tetrasulfonic acid tetrasodium salt copper phthalocyanine (GR–TSCuPc) for combination of PTT and PDT, using fabricated GR to act as a PTT agent and TSCuPc to act as a PDT agent. In vitro results show that the PT effect of GR–TSCuPc is higher than that of free TSCuPc, which indicates that combination of PTT and PDT shows better anticancer efficacy [74].

Golavelli et al. [75] designed a magnetic/fluorescent graphene-silicon naphthalocyanine bis theranostic nanocarrier to use in combination with a PTT and PDT reagent via dual modal imaging. In vitro studies and singlet sensor green experiments confirm the generation of $^1O_2$ and killing efficiency of MFG-SiNc4 to be approximately 97.9%.

4.3 Functionalized graphene

Due to their sp^2 carbon NMs, CNs like graphene are highly hydrophobic, making functionalization necessary before the materials can be used for biomedical applications. Methods of functionalization, including covalent and non-covalent strategies, vary in their effectiveness. Covalent modification involves the conjugation of hydrophilic functional groups and protective polymers such as PEG [76]. Functionalized graphene obtained using the covalent strategy is usually stable. Non-covalent functionalization involves using electrostatic forces, π-π interactions, and hydrogen bonding.

Yang et al. [77] did a study to determine the in vivo behavior of PEG-coated nano-graphene (NG) sheets in mice by a fluorescent labeling method for cancer. To treat tumor, PEGylated NG sheets appears to be an excellent in vivo tumor NIR PTT agent without showing noticeable toxic effects. The use of strong optical absorbance of NG sheets in the NIR region for in vivo PTT showed efficient tumor ablation and low energy NIR laser irradiation on tumor after intravenous administration. Therefore, PEGylated NG sheets highly effective tumor passive targeting. In vivo fluorescence imaging shows surprisingly high tumor uptake of NG sheets in vivo models. According to Yang and co-workers examination, in vivo application and potential toxicology of graphene was first explored in animal models. Previous studies show that in the PDT $^1O_2$ generation plays a significant role in the effectiveness to kill tumors. In another study, methylene blue functionalized GO show excellent $^1O_2$ generation at 785 nm laser irradiation [78].

4.3.1 Nano-graphene oxide

It is known that NG and nano-graphene oxide (NGO) have remarkable photothermal impacts owing to their effective light-to-heat conversion when compared to other carbon allotropes under low-power NIR irradiation [79].

NGO systems have also been used to successfully reduce the number of cancer cells. Hai Qing et al. [80] designed and synthesized PEG-modified NGO and loaded the PS-ZnPc into the system via π-π stacking to show the possibility of utilizing NGO in PDT. The viability of MCF-7 carcinoma cell line was tested under various conditions, from a 3.8 to 60 mg/L concentration of ZnPc. Cancer cell viability was lowered from 85 to 60% after light irradiation. These findings indicate that there are potential applications of PEG-conjugated NGO in PDT. Another study observed how the size and surface chemistry of graphene affected its in vivo performance in PTT. The PTT agent nRGO-PEG was observed to have 100% tumor elimination power after injection [81].

In 2013, Shi et al. [82] developed a graphene-based magnetic and plasmonic nanocomposite called GO-IONP-Au-PEG and showed its exceptional photothermal activity and ablation of tumor, arguing that graphene-based NMs have great potential in cancer theranostics. Sahu et al. [83] prepared a pluronic block NGO loaded into high hydrophilic and positively charged PSs methylene blue. Their work showed that the PS released more efficiently in acidic pH levels. Zhang et al. [84] combined chemotherapy and PTT in one system by developing DOX-loaded PEGylated graphene oxide (NGO-PEG-DOX) complex. Their results showed that neither DOX chemotherapy nor NGO-PEG PTT alone was effective, and NGO-PEG-DOX was superior to both.

4.3.2 Reduced nano-graphene oxide

Recent studies have shown that reduced graphene oxide (rGO) is effective in vitro DDS and in vivo photothermal heating. Compared to GO, rGO has dramatically enhanced NIR absorption, so that Robinson et al. [85] developed biocompatible rGO sheets as PTT agents. Functionalized nano-rGO allowed for peptide conjugation to target cancer cells through selective photo ablation at a low dose. This was the first study that used rGO and non-covalent PEGylation and established it as an effective PTT agent.

Following this study, Yang et al. [86] designed a novel rGO and iron oxide nanoparticle (ION) functionalized with PEG (rGO-ION-PEG) in 2012. Tumors in mice were treated using rGO-ION-PEG and an 808-nm laser source. The results demonstrated an instantaneous shrinkage of the volume of the tumors. RGO could be an improvement over GO with enhanced and modified photothermal effect. Kim et al. [87] designed a new PEG-BPEI-rGO system where nanocarriers escape the endosome by photothermally inducing and killing more cancer cells through NIR irradiation. rGO nanomesh (rGONM-PEG) is an ultra-efficient in vivo PTT agent because it exhibits about 4.2- and 22.4-fold higher NIR absorption at 808 nm than rGONP-PEG and GO, respectively. In addition, in vivo fluorescence imaging has demonstrated high selective tumor uptake of rGONM-PEG-Cy7-RGD in mice bearing U87MG cells [88].

A novel study with rGO has resulted in the development of a class of targeted PTT agents PEG-g-polydimethylaminoethylmethylacrylate-hyaluronic acid-rGO (PgP/HA-rGO) [89]. This PTT agent generated the highest photothermal heat on the tumor surface and led to the ablation of the size of tumor from 225 to 50 mm^3 within 10 days after therapy [89]. To improve this PTT effect, Sharker et al. [90] designed a NIR-sensitive, pH-dependent hybrid composite of indocyanine green-GO (ICG-rGO) that showed a photothermal heat generation capability in the pH range from 5 to 7.4 and an improved in vitro targeted cancer cell photothermal destruction compared with free ICG.

Combinational therapy has been known to be more effective in cancer treatment than monotherapy. Chen et al. [91] combined radiotherapy and PTT to develop a combinational

therapy that involved the radionuclide $^{(131)}$I labeled rGO. This combines the strong NIR absorbance of rGO and the X-ray radiation of radionuclide $^{(131)}$I to kill cancer cells. The rGO exhibits strong NIR absorbance, at the same time, radionuclide $^{(131)}$I emit X-ray and both of them induce cancer cell killing. ^{131}IRGO-PEG can deliver for both PTT and RT to achieve cancer combinational therapy effect. In another work, Sheng et al. [92] constructed integrated photoacoustic and PTT platforms with protein-based nano-rGO. Administration of NGO exhibited significant enhancement of acoustic signals on the tumor regions and usage of NIR led to ablation in cancer cells. To further enhance photoconversion efficiency and improve PTT of tumors, Gao et al. [93] formed hybrid NMs called CPGA that possess high tumor accumulation and photoacoustic signals. Moreover, Wang et al. [94] combined chemotherapy and PT using mesoporous silica nanoparticles (MSNs) as a drug carrier with rGO. MSN-rGO-FA nanocomposites killed 68% of HEp-2 cells in synergistic therapy, whereas they killed only 54% in PTT and 33% in chemotherapy alone.

4.4 Graphene oxide

As a potential carrier system, GO exhibits remarkable properties such as mechanical, electronic, thermal, electrochemical, transparency, and biocompatibility because of its hydrophilic nature similar to graphene [95]. On the other hand, because of the presence of numerous oxygen-containing hydroxyl and epoxy groups, GO has distinct characteristics that greatly differentiate it from graphene [96]. The high surface of GO sheets can be used to load drugs [97]. The absorbance of GO extends from UV wavelength to the NIR region (at 808 nm). GO can be used for cancer cell treatment due to its photothermal properties. However, dispersion of GO is not easily achieved in bio-applications because of the chemical interactions between GO and proteins/salt in serum [98]. GO has toxic effects on macrophages; it plays a significant role in lipid peroxidation and membrane damage as illustrated in Fig. 7.

The toxicity of GO is based on the size of the sheet. GO with smaller sheet size demonstrates lower toxicity. Nevertheless, Rosli et al. [100] have uniquely manufactured GO nanoplatelets (GONPs) from well-known stacked graphite nanofibers with a base of 50 × 50 nm^2 for toxicity and drug potentiation examinations. In their study, GONPs are loaded with chemotherapeutic drug cisplatin (CP), which is used in human lung cancer cells (A549 cells). According to their examinations, they found that not only GONPs can act as drug carriers, but they were also able to show the anticancer effect of CP in lung cancer cells.

Zhang et al. [101] prepared a dual-sensitive DDS based on GO and it was also loaded with proapoptotic peptides. Particularly, various cell apoptosis peptide (KLAKLAK)2 (KLA) was anchored on the surface of GO via a disulfide bond in order to achieve GO-SS-KLA. After that, the anticancer drug (DOX) was loaded on GO. At the final stage, bovine serum albumin (BSA) was used to coat the GO carrier system in order to achieve a biological medium-stable GO-based DDS, DOX@GO-SS-KLA/BSA. The result of their study illustrates that KLA and DOX are able to respond to the reductive and pH stimulus inside the cells. Moreover, the stability results predict that DOX@GO-SS-KLA/BSA was stable in water for more than 8 days and in 10% fetal bovine serum for at least 6 days. The established DOX@GO-SS-KLA/BSA shows great potential as DDS for the co-carrying system of different therapeutic agents.

In DDS, GO plays a more attractive role in terms of its large π-conjugated structure which can interact with the aromatic drug. According to previous studies, hypocrellins are the second generation of PSs and present high PDT effects on many cancer types [102]. However, some limitations occur in clinical usage of hypocrellins. The first-time photodynamic activity of GO-hypocrellin A (HPA) was studied in 2011 by Zhou et al. [103] and they showed that the amount of HPA loaded onto GO was significantly high. The GO-HPA complex can generate $^1O_2$ when excited by irradiation with light of appropriate wavelength. In vitro studies exhibited that GO-HPA taken by tumor cells resulted in significant cell death. Hence, GO-HPA complex is promising for use in clinical PDT. The same group did another study in 2012 [104], where an efficient loading amount of 2 mg/mg HPB on GO was observed for hypocrellin B. In vitro tests showed that there was active uptake HPB-GO into tumor cells and important damages were observed upon irradiation.

Recently, examinations showed that when Ce6 is combined with NMs, it has excellent water solubility and improves PDT destruction of cancer cells. In order to show the PTT effect of graphene was used to support the delivery of Ce6 when exposed to NIR and further improve PDT efficacy on the cancer cells, a combination of graphene and PEG is used for Ce6 delivery [105]. In one study, FA-conjugated GO was developed to target and achieve higher specificity of PDT. PSs Ce6 efficiently loaded into the system. Accumulation of Ce6 in cancer cells significantly increased, thereby demonstrating a remarkable PDT effect for MGC803 cells upon irradiation. Suggesting that FA-conjugated GO-loaded Ce6 is effective in targeting PDT [106]. However, this type of study causes loading inefficiency. To address this issue, Zhou et al. [107] developed a synergistic combination of chemo-PDT by chemotherapy drug (SN-38) and HPA loaded into GO complex. Following to mentioned work, the hyaluronic acid (HA)-GO conjugate system is prepared and is loaded into Ce6 as PSs in another study [106]. Cellular internalization of this complex is much more effective than free Ce6. Furthermore, PDT efficiency of HA-GO-Ce6 enhanced ten folds compared to free Ce6 [108]. In 2015, Liu

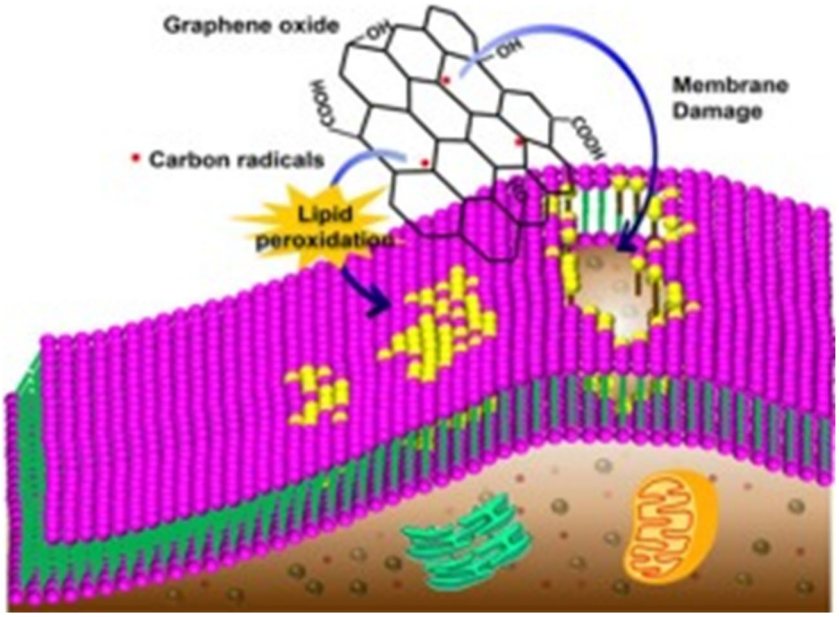

Fig. 7 Toxic effects of GO on macrophages [99]

et al. [109] also produced of graphene from natural graphite with Ce6, which is a promising composite for PT. High drug loading capacity of 160 wt% was observed, ten times larger than functionalized GO. Moreover, GO-Ce6 tumor cell killing efficiency is 6–75 folds greater than free Ce6. In another remarkable research, Dembereldorj et al. [110] tested AuNR-PEG-GO for a photothermal platform both in vitro and in vivo. Irradiation with a Xenon lamp light and treatment with the AuNR-PEG-GO, epidermoid carcinoma cells shows cell viability reduction by approximately 40% compared to the cells treated with only AuNR-PEG-GO. Moreover, in brain cancer therapy, a biocompatible porphyrin functionalized graphene oxide can be used (PGO). The latter is two times more stable than rGO, and the efficiency of photothermal conversion of PGO is raised by 89%, thereby causing ablation of brain cancer cells in vitro [111].

Extensive previous studies claim that GO is an efficient delivery platform for cellular imaging. In 2012, Hu et al. [112] reported that novel QD-tagged rGO (QD-rGO) could be used to image tumors in PTT. The heat generated from QD-rGO causes an increase in the temperature (cell death) and degradation of QDs which provides an indicator of PTT. After this work, Wang et al. [113] developed UCNPs-NGO/ZnPs for combinatorial PDT and/or PTT theranostic platforms. These nanocomposites used as a UCL illustration probe but at the same time create cytotoxic $^1O_2$ under light excitation for PDT and also convert laser energy into thermal energy for PTT. Furthermore, theranostic agent fabricated by loading ION into poly (lactic acid) (PLA) and surface modification with GO microcapsules. Due to the strong absorption of NIR, microcapsules kill cancer cells. Moreover, they found that the photothermal effect could be enhanced by external magnetic field. This development is promising to integrate both imaging and therapy for cancer theranostic [114]. In addition, using the solvothermal method PEG-BaGdF5-GO complex formed as both imaging and PTT. Enhanced NIR and photothermal stability of PEG-BaGdF5-GO complexes result in efficient ablation on tumor cells [115].

The efficiency of GO-green platinum nanoparticles (GO-PtNPs) on human prostate cancer cells is uncertain. Gurunathan et al. [116] synthesized GO-PtNPs nanocomposites to understand their effect on prostate cancer cells. The cytotoxicity of GO-PtNP was raised through lactate dehydrogenase release and membrane integrity loss. Oxidative stress induced by GO-PtNPs raised protein carbonyl malondialdehyde and nitric oxide ingredients. The powerful ROS generation impaired the cellular redox balance and eventually exchanged mitochondria by reducing the ATP level and the membrane potential. The toxicity to cancer cells was connected to the expression of proapoptotic genes and reduced levels of anti-apoptotic genes. Their study showed that p53 and p21 activation in GO-PtNP–treated cells led to genotoxic stress, which also caused apoptosis. GO-PtNPs are both cytotoxic and genotoxic. Tumors are more sensitive to GO-PtNPs than to GO nor PtNPs. Moreover, GO-PtNPs have a suitable and effective cancer therapeutic system. The studies about functionalized GO used for cancer therapy are summarized in Table 1.

5 PT of CNTs

Multi-walled carbon nanotubes (MWCNTs) were first obtained by Iijima in the 1990s, using the arc-discharge evaporation method [118]. After 2 years, Iijima and Lchihashi [119] and Bethune et al. [120] obtained single-wall carbon nanotubes

Table 1 Summarize of functionalized GO that is used for cancer therapy

Nanosystem	Modified materials	Morphology	Size	Light source	Loaded agent	Conjugation	Cancer cell	Result	Reference
GO-fMLP	N-formyl-methionyl-leucyl-phenylalanine (fMLP)	A lamellar structure	600 ± 300 nm	-	DOX	Hydrogen bonding and electrostatic interactions	Cervical carcinoma cells and human cervix cancer cell line HeLa cell	The hybrid system of GO-fMLP is susceptible to increase myeloperoxidase-mediated degradation.	[48]
GQDs	-	Spherical-shaped	56.6 ± 8.7 nm	Blue light at 470 nm	-	-	U251 human glioblastoma cells	GQDs and blue light (470 nm) generate 1O2 and cause cell death.	[69]
NGO-mPEG	Polyethylene glycol (PEG)	Spherical-shaped nanoparticles	200 nm	492 nm	ZnPc	π-π stacking interaction and hydrophobic interactions	MCF-7 carcinoma cell line	Cancer cell viability was lowered to 60% after light irradiation, however remained at 85% without light irradiation.	[80]
GO-IONP-Au-PEG	Iron oxide nanoparticles (IONPs)-gold-PEG	Spherical-shaped nanoparticles	200~600 nm	NIR laser at 808-nm laser	-	-	The murine breast cancer 4T1 cells and human carcinoma KB cells	The prepared NP has high stability in physiological environments and no significant in vitro toxicity.	[82]
NGO-PEG-DOX	PEG	Spherical-shaped nanoparticles	100 nm	NIR laser at a 808-nm laser	DOX	π-π stacking interaction	EMT6 cells	Neither DOX chemotherapy nor NGO-PEG PTT alone was effective, and NGO-PEG-DOX was superior to both.	[84]
Nano-rGO-PEG-RGD	PEG-Arg-Gly-Asp (RGD)	Single-layered nanosheets	~ 20 nm	NIR laser at a 808-nm laser	-	-	U87MG cancer cells	This was the first study that used rGO and non-covalent PEGylation and established it as an effective PTT agent.	[85]
GONP-CP	-	Nanofiber-nanoplatelets	37 nm	-	Cisplatin (CP)	Covalent binding	Lung cancer cell line (A549 cells)	Not only GONPs can act as drug carriers, but they were also able to show the anticancer effect of cisplatin in lung cancer cells.	[100, 117]
GO-HPA	Hypocrellin A (HPA)	A lamellar structure	200–400 nm	From 350 to 800 nm	Hypocrellin A (HPA)	Non-covalent bonding	Human cervix cancer cell line HeLa cell	The amount of loaded HPA onto GO significantly high and GO-HPA complex can generate $^1O_2$	[103]

Table 1 (continued)

Nanosystem	Modified materials	Morphology	Size	Light source	Loaded agent	Conjugation	Cancer cell	Result	Reference
								when excited by irradiation with light of appropriate wave-length.	
GO-PEG-Ce6	PEG	Spherical shaped nanoparticles	Less than 50 nm	NIR laser at 808-nm laser	Chlorin e6 (Ce6)	Supramolecular π-π stacking inter-action	The human nasopharyngeal epidermal carcinoma KB cell line	Graphene can be used for potential multifunctional cancer therapies.	[105]
HPA/SN-38/GO	-	A lamellar structure	-	470 nm LED	7-ethyl-10--hydroxycam-ptothecin (SN-38), hypocrellin A (HPA)	Hydrogen bond and π-π stacking inter-action	Lung cancer cell line (A549 cells)	Combinational therapy enhances the anticancer efficiency in vivo.	[107]
UCNPs-NGO/ZnPs	PEG	Spherical-shaped nanoparticles	28 nm and 40 nm	NIR laser at a 808-nm laser	ZnPc	π-π stacking interaction	Nasopharyngeal epidermal carcinoma KB cell and human cervix cancer cell line HeLa cell	Due to the strong absorption of NIR, microcapsules kill cancer cells and the photothermal effect enhanced by external can be a magnetic field.	[113]

(SWCNTs) using the same procedure. CNTs have outstanding electrical, optical, and thermal characteristics. They can influence the electric field in their localized surrounding which enhances the absorption of electromagnetic energy and creates rapid heating of the tube [120].

5.1 Functionalized CNTs

The proper surface functionalization of CNTs renders them biocompatible and enables them serve as efficient cancer DDS [98]. The f-CNTs are a highly promising drug delivery system because of their ability to cross the biological barriers of the cell. In general, the process of functionalization requires organic solvent or water solubility, enhancement of functionality, dispersion, and compatibility, but CNTs also require functional groups to carry simultaneously several moieties for targeting, imaging, and therapy [121]. Attachment can be achieved via either covalent or non-covalent bonding. Non-covalent functionalization preserves the electronic structure of the nanotube and does not lead to noticeable toxicity in animals treated. The preferred compound for functionalization is PEG, which increases the dispersity in aqueous solution and the biocompatibility of CNTs [122]. However, the use of CNTs in nanocomposites to date has been limited by challenges in processing and dispersion, and their prohibitively high cost [123]. In 2009, Erbaş et al. obtained the multifunctional PDT agent pyrenyl-functionalized distyryl-bodipy non-covalently attached to SWCNTs. This PS agent generated $^1O_2$ when it was excited with a red LED array that produced light of a 660-nm wavelength [124]. Functionalization is important because it is believed that the rising temperature denatures proteins and leads to tumor eradication. It was also previously known that CNTs display strong absorption over a wide range of frequencies of electromagnetic radiation, including visible light, NIR light, and even radio irradiation. To prove this, a photothermal and fluorescent agent was synthesized by the conjunction of pyrene-based PEGylation of SWCNTs. The agent was water-soluble, generated heat under NIR of 5 W/cm^2, which causes significant cell damage and suggests that Py-PEG-SWNT can serve as a photothermal agent in PTT. Furthermore, it was found that both synthesized Py-PEG and Py-PEG-SWCNTs complexes exhibited high fluorescence intensity at 382 and 395 nm, suggesting that Py-PEG-SWCNTs are able to treat patients undergoing cancer therapy. Another study investigated the heat and light dual responsive function of SWCNTs. Poly(N-isopropylacrylamide) (pNIPAM) was grafted to Cur (Cur-pNIPAM), and SWCNTs wrapped with this thermo-responsive Cur-pNIPAM was developed (SWCNTs/Cur-pNIPAM complex). This complex showed the reversible dispersion coagulation action in response to temperature which leads to a catch-and-release action of a porphyrin derivative and it is expected to be applicable to novel PDT control techniques [125]. The in situ synthetic method was used to non-covalently functionalize noble metal nanoparticles and obtain SWCNTs-Au-PEG and SWCNTs-Ag-PEG nanocomposites. The gold shell grown on the nanotube surface of the SWCNTs-Au-PEG-FA nanocomposite dramatically increases the cancer-killing effect due to its strong surface plasmon resonance absorption. In vitro study cells treated with SWCNTs-Au-PEG-FA, SWCNTs-Au-PEG, SWCNTs-PEG-FA, and SWCNTs-PEG with laser irradiation at 808 nm for 5 min showed that SWCNTs-Au-PEG-FA had the greatest effect on cell death after laser irradiation [126].

5.1.1 In vivo studies of f-CNTs in cancer therapy

CNTs are an outstanding option for PT because of their high capacity to hold drugs, great cell membrane permeability, and enhanced cellular uptake. Over time, numerous studies have shown the impact of f-CNTs in cancer therapy by using models such as mice, human breast cells, and solid malignant tumors [127]. The strong optical absorption and high photon-to-thermal energy conversion efficiency of CNTs in the NIR region combined with a high-absorption cross-section make CNTs suitable candidates for PTT [98]. The destruction of breast cancer cells by non-covalently attaching monoclonal antibodies (MAbs) against membrane markers: insulin-like growth factor 1 receptor and human endothelial receptor 2. The antibodies were attached using π-π interactions of the pyrene rings to SWCNTs [128]. Because the EPR effects are universal in solid tumors, CNTs loaded with drugs can extravasate in tumor tissues over time; the concentration in tumor will reach several folds higher than that of the plasma [129].

In 2009, Moon et al. [130] demonstrated the photothermal effect of PEG-SWCNTs with light irradiation and examined in vivo destruction of solid malignant tumors. Photothermally treated mice showed the obliteration of tumors, while control groups had tumors that continued to grow. The tumors in the photothermally treated mice were excreted in approximately 2 months by either the biliary or urinary pathways. This led to the claim that PTT with SWCNTs is a successful cancer therapeutic approach.

Liu et al. [131] studied the effects of time and dosage on the efficiency of PTT using SWCNTs. They studied the relationship between the polymer-coated surface and in vivo behaviors of SWCNTs. The group used Raman spectroscopy to establish blood circulation half-life and found that PEG-SWCNTs have a blood circulation half-life of 12–13 h, relatively low RES and high tumor uptake with skin accumulation, giving them great potential for cancer treatment. In vivo studies conducted using tumor-bearing mice found that groups treated with only radiation or SWCNTs had similar tumor regrowth patterns, while groups which were treated with SWCNTs that had optimized surface coated with PEG showed that the complex was a powerful PTT agent. Liu et al. examine light-sensitive SWCNTs were modified with Ce6

and PEG for tumor treatment. In vivo studies showed that SWCNTs-g-Ce6 and SWCNTs-g-Ce6-g-PEG had greater accumulation of Ce6 in the tumor sites due to their enhanced permeation and retention effects, demonstrating their value in the treatment of solid tumors.

Anteris et al. [132] studied the viability of breast cancer cells treated with SWCNTs containing antibodies. The viability of the cells was affected by the concentration of f-MWCNTs-ab, irradiation time, and settling time after NIR irradiation. After conducting the Alamar Blue cell viability test, it was concluded that PTT using f-MWCNTs-ab led to 65–79% better destruction of breast cancer cells compared to treatment using only f-MWCNTs. The EtBr cell viability test produced the same results as the Alamar Blue test, and also suggested possible cell destruction mechanisms.

5.2 Single-walled carbon nanotubes

The high resolution in vivo imaging, deep-tissue penetration in NIR, combined with strong tumor accumulation and intrinsic photoluminescence make SWCNTs promising cancer theranostic agents. The SWCNTs with light absorption in the NIR range allows PTT at much lower laser powers than those needed for plasmonic NMs [133].

In 2011, Zhou et al. [134] explored a novel therapy that used SWCNTs to target the mitochondria in breast cancer cells. Targeting the mitochondria of cancer cells in promising cancer treatment because mitochondrial depolarization and the activity of cytochrome c and caspase 3 lead cells to go into apoptosis. Studies in mice showed that those treated with lasers and SWCNTs-PEG had a survival rate of 75%, while the group that received only laser treatment had a survival rate of only 31.25%. It was claimed that the mitochondria-targeting SWCNTs enhanced the PTT destruction of tumor cells. One year later, a study showed the synergistic photothermal and immunological effects the modified nanotube system had on the treated cancer cells. The SWCNTs-GC complex included a strong immunoadjuvant called glycated chitosan (GC), and when the complex was exposed to radiation, the GC served both DAMPs and PAMPs, enhancing the immunogenicity of tumor cells and presentation of tumor antigens led to synergistic PTT immunological reaction. SWCNTs retained the optical properties of SWCNTs and immunological properties of GC when treated with lasers in mouse mammary tumor cells. The absorption rate of the SWCNTs-GC complex was 89.2%, which was higher than the 73.1% absorption rate of the SWCNTs-PEG complex that is commonly used as a surfactant. Interestingly, when one side of tumor was treated with SWCNTs-GC, the other untreated side was affected. This indicates that SWCNTs-GC complex prerequisites to induction of effective antitumor immune response. Most effective SWCNTs-GC modalities have been higher survival rates and strong tumor suppression in contrast to others [135]. In 2015, Zhou et al. [136] tested a DOX-loaded SWCNTs-GEL both in vitro and in vivo using NIR hyperthermia treatment to provide a new perspective into gastric cancer. They showed that incorporating NIR irradiation in DOX/SWCNTs-GEL treatment led to greater cancer cell apoptosis than using free DOX. The free DOX-treated group showed an average tumor growth ratio of 166%, but the DOX/SWCNTs-GEL–treated group showed shrinkage of tumor size of 61.3% of original volume. SWCNTs-based hydrogel had the strongest tumor suppression rate, while without NIR radiation SWCNTs-GEL did not produce any inhibition effect.

Hood et al. [137] applied this information to breast cancer treatment by using a human protein called annexin V (AV), which binds anionic phospholipids expressed externally on the surface of the tumor cell surface was conjugated with SWCNTs. In vivo studies produced encouraging results that a majority of BALB/c female mice implanted with 4T1 murine mammary tumors were treated with 0.8 mg SWCNTs kg^{-1} and NIR irradiation at a wavelength of 980 nm showed complete disappearance of the implanted tumors 11 days after irradiation.

Moreover, to evidence CNTs more subsequently, Marches et al. [138] coupled CNTs with tumor-specific MAbs. Using flow cytometry, immunofluorescence, and confocal Raman microscopy, they found that anti-Her^{2+}-CNTs effectively bind, whereas the control, MAb-CNT, did not bind. More importantly, cells that internalized the Her^{2+} and CNTs were more sensitive to NIR-mediated photothermal damage than cells with CNTs on their surface.

5.2.1 Applications of SWCNTs

SWCNTs produce novel hybrid NMs which and enhance chemical functionalization and solubility for potential applications in biological detection, DDS, PT, and biomedical imaging [139]. In 2010, Huang et al. injected SWCNTs into mice tumors and irradiated them with 785 nm NIR radiation at a moderate power of 200 mW/cm^2 (120 J/cm^2) to remove squamous cell carcinomas. Raman spectroscopy was used to observe SWCNTs distribution in situ and it was found that the SWNTs remained localized in the tumor even 3 months after injection [140]. In 2012, Xiao et al. [141] [141] developed an efficient nano-PS delivery system by conjugating Ce6 and SWCNTs, then wrapping the complex with chitosan to improve water solubility and biocompatibility. A WST-1 assay was used to determine the PDT effect of chitosan-Ce6-SWCNTs by detecting the viability of HeLa cells after irradiation. The complex had a higher cancer-killing effect (and thus a more desirable pharmacological outcome) than a free Ce6 complex.

SWCNTs have strong Raman scattering due to their sharp electronic density of states. Beca et al. [95] used this property

of SWCNTs to design a chemically novel hybrid NMs to treat breast cancer. They used a gold nanopopcorn–attached SWCNT to target cancer tissue. The aptamer-conjugated hybrid NMs show Raman signal intensity of SWCNT D and G bands by three orders of magnitude. When S6 aptamer–conjugated hybrid NMs were attached to SK-BR-3 cancer cells, they were exposed to 785 nm continuous NIR radiation at 1.5 W/cm^2, causing cellular damage that killed soft cancer cells within 10 min. This hybrid conjugation has an enormous potential application in rapid detection and PTT of clinical samples. Another striking application of CNTs is as a contrast agent. Normally, ideal contrast agents do not identify tumor mass but provide non-invasive therapy opportunities. To overcome this issue, Antaris et al. [142] developed biocompatible, SWCNTs that have the properties desired in theranostic agents. Using the ultra-pure SWCNTs reiterated the pharmacokinetics, imaging, and photothermal capabilities of bulk SWCNTs, unambiguously tumors imaged and heated to 50 °C with an intravenous injection of ~ 4 μg of SWCNT material. They claimed that ultra-low-dose, high-efficiency SWCNTs are ideal for nanomedicine. Modifications of SWCNTs using chemical functionalization and conjugations are necessary to enhance solubility and produce novel hybrid materials that are potentially suitable for many applications. In 2012, Meng et al. [143] demonstrated an easy method to obtain SWCNTs coated with AuNPs by using a thiol-functionalized IL as a type of glue and characterized by HR-TEM-Raman and UV/Vis absorption spectroscopy. The TEM results showed that the SWCNT-IL-Au^{+2} material internalized in the lysosomes of HeLa cells did not enter the nucleus. HeLa cells that were cultured with SCWNT-IL-Au^{+2} material and then exposed to a 2 W laser diode with a wavelength of 808 nm for 15 min, the SWCNT-IL-Au^{+2} material changed color to orange or red, indicating that the cells were undergoing apoptosis. In another study, Ogbodu et al. [144] examined the effect of SWCNTs conjugation with zinc monoamino phtalocyanine-FA form (ZnMAPc-FA-SWCNTs) on melanoma cells. Melanoma cells treated with ZnMAPc-FA-SWCNTs and then irradiated with a 676-nm laser that had a power density of 98 mW/cm at 5 J/cm showed 63% cell death. It was also discovered that ZnMAP-FA caused 60% cell death, but SCNTs-FA did not serve as an effective PT agent. ZnMAPc-FA-SWCNTs produced 0.18 $^1O_2$ and ZnMAPc-FA produced 0.48 $^1O_2$, which suggests that ZnMAPc-FA-SWCNTs can produce relatively little $^1O_2$ but still be an effective PDT agent. The same team conducted another study to examine the photophysical properties and photodynamic activity of the synthesis of zinc mono carboxy phenoxy phthalocyanine conjugate with spermine (ZnMCPPs-spermine) and the effect of ZnMCPPS-spermine-SWCNTs on breast cancer. PDT results showed that ZnMCPPs leads to 64% cell viability while ZnMCPPs-spermine led to a 97% cell viability and ZnMCPPS-spermine-SWCNTs led to a 95% cell viability. Interestingly, it was found that the O_2 generation of ZnMCPPS-spermine-SWCNTs was lower than that of the ZnMCPPs-spermine complex because the Pc-spermidine conjugate reduced PDT activity when combined with SWCNTs [145]. Integration of multimodal treatment in cancer therapy can enhance efficiency and cause synergistic effects. A biomodal system is constructed (Ru@SWCNTs) which is Ru (II) complex-functionalized with SWCNTs to photothermal and two-photon PDTs (PTT-TPPDT) in cancer treatment. When the PTT effect of Ru (II) at a 808-nm laser irradiation was observed, it was found that it produces $^1O_2$ in vivo and can be used as TPPDT. Cells were incubated with Ru (II) complexes, SWCNTs, and Ru@SWCNTs at a 808-nm laser at a power density of 0.25 W/cm^2 for 5 min to examine the effects of Ru@SWCNTs composites on the kinetics of two-dimensional and three-dimensional tumor cells. Results indicated that Ru@SWCNTs destruction of cancer cells was more effective than free SWCNTs and Ru (II). In 3D tumor cells, the cell viabilities of the multicellular tumor spheroids after 5 min of laser irradiation were only 5%. Ru@SWCNTs exhibited excellent bimodal PTT and PDT effects in cancer modals [146].

5.3 Multi-walled carbon nanotubes

MWCNTs are polymers of pure carbon that are chemically reactive because of the rich chemistry of carbon [147]. Due to their high aspect ratios, MWCNTs have unique electronic and mechanical properties that allow the easy modification of structure and optimization of solubility and dispersion, spurring their innovative applications in biomaterials, electronics, and chemical processing [120]. It has been known that MWCNTs can be used as a cancer therapy agent because they release vibrational energy when exposed to NIR irradiation. In 2009, MWCNTs conjugated with GD2 MAbs were used to cure neuroblastoma cells. Anti-GD2-linked CNTs were broadly internalized in the cells and then the cells were exposed to 800 nm NIR laser for 10 min. When they were examined with calcein-AM dye, it was observed that the neuroblastoma cells had undergone necrosis. Anti-GD2-linked CNTs have been utilized as a therapeutic coupling agent in killing neuroblastoma cells by generating heat [148]. Polyamidoamine dendrimer modified MWCNTs have been explored as a highly efficient delivery system for PS 5-aminolevulinic acid (5-ALA) to MGC-803 tumor cells. When 30 μM 5-ALA-dMNTs were irradiated with a light, they caused approximately 70% loss of cell viability, demonstrating a clear PDT effect [149]. When treating colorectal cancer, MWCNTs have to be applied during surgery because they cannot be introduced intravenously and then travel to the peritoneum. Instead, during the surgery, a chemotherapic agent is used to fill the abdomen and then the individual tumor nodules are treated with PT. This involves rapidly heating the

colorectal cancer cells to 42 °C, using MWCNTs as a heat source in the presence of the drugs oxaliplatin and mitomycin C. Preliminary result emphasizes the potential of the fast bench to bedside clinical therapeutic agent with MWCNTs and chemotherapeutic agents. Conducted after many types of research, in order to deal with colorectal cancer FA conjugated to MWCNTs. Because they are known to produce the folate receptor, which is found in tumor location. Developed spectrophotometric method to quantify the mass of MWCNTs bound to cells and showed that FA-targeted MWCNTs binds with a high affinity to colorectal cancer in spite of untargeted MWCNTs. Moreover, FA-functionalized MWCNTs stimulated by a 1064-nm light led to a reduction in colorectal cancer cell viability. These results indicated that an increase in therapeutic index of MWCNT by FA-targeted MWCNTs-induced PTT [150]. Failure caused by single therapy propels to improve combinational therapy methods. In 2016, Marangon et al. [142] constructed a combination of PTT and PDT nanosystem–based MWCNTs with a PS of m-tetrahydroxyphenylchlorin for cancer treatment. When irradiated with a 650-nm light, the mTHPC/MWCNTs showed high fluorescence and phototoxic features. Increasing cellular uptake enables greater thermal activations. A cell viability test, TEM, imaging cytometry confocal microscopy, and genomic analysis of 84 genes all showed that oxidative stress was evident in the affected cells. This emphasized that mTHPC/MWCNTs has an important role in inducing a signaling pathway in PTT/PDT that triggers apoptosis. The oxidative response led to a sharp increase in the number of proteins that were formed in ROS generation.

6 PT for fullerenes

In 1985, a third carbon allotrope was added to the list along with diamond and graphite: C_{60} that has an interrupted icosahedron soccer ball–like shape consisting of 12 pentagons. The extended π-conjugated system available in C_{60} molecule gives it an exceptional ability to absorb visible light. When C_{60} absorbs light, it enters its singlet excited state and undergoes an intersystem crossing into the triplet state. Some molecules of C_{60} in the triplet state are quenched by molecular O_2 and generate $^1O_2$, while others generate superoxide anion radicals, especially when in the presence of a reducing agent. Unspoilt C_{60} and C_{60} derivatives generate ROS by illumination, which makes them good candidates for PT. There has been remarkable progress in developing functionalized C_{60} for anticancer drugs and diagnostic agents [151]. The functionalized C_{60} used to physisorbed on the three-dimensional mesoporous graphene macro assemblies electrodes as illustrated in Fig. 8.

The drug complex with nano-size was investigated to evolve the efficiency of cancer therapy, finalize it with nano delivery and PDT. Grebinyk et al. have examined that nanomolar amounts of a non-covalent nano complex of the drug as DOX with carbon nanoparticle C_{60} were enforced in different molar ratios as 1:1 and 2:1 M ratios. This system is exploiting C_{60} both as DDS and as PSs. According to the fluorescence microscopy analysis, the in vitro tumor model cultured with nano complexes illustrated DOX's nuclear and C_{60}'s extranuclear localization. When cells were applied to C_{60}-DOX with 2:1 M ratio and irradiated (405 nm), the high cytotoxicity of photo-irradiated C_{60}-DOX destroy cancer cells in vitro [153].

6.1 Functionalized fullerenes

Pristine fullerenes are highly hydrophobic, which may hamper their biological applications. To overcome this shortcoming, functionalization of the surface with some hydrophilic functional groups is thus needed to make them more soluble in water and biological solutions [154]. As with other nanoparticles used in PS delivery, C_{60} has also been modified to carry imaging agents. To demonstrate this mechanism, Ikeda et al. designed light-harvesting "antenna" molecules with liposomal PSs and dense C_{60} into lipid membrane bilayers [56]. The liposomal PS showed improved photodynamic activity when exposed to light wavelengths between 610 and 740 nm toward human cancer cells via the photoenergy transfer from photoactivated antenna molecules to C_{60}. The concept of light-harvesting liposomal PS of LMIC60 shows remarkable promise in the field of medicinal chemistry [155].

Polyhydroxy fullerenes (PHFs) exhibit photoacoustic and photothermal properties for imaging and cancer therapy. PHF has numerous advantages, including biocompatibility, biodegradability, and water solubility. When PHF nanoparticles were exposed to NIR during a study, they caused a 32% decrease in tumor area due to their ability to inhibit tumor growth and regulate the immune system. It was also found that PHF-containing chitosans provide excellent photoacoustic contrast [156]. PHF heat and generate sound waves under low-intensity laser irradiation. PHF is unique as photothermal properties of PHF are not dependent on the wavelength of irradiation [157]. PHF is 1.3 nm in size and is able to be easily excreted in urine; on the other hand, larger NMs such as CNTs and AuNPs typically exceed the renal excretion limit of 5.5 nm [158]. PHF found to be heated to their ignition temperature by exposure to low-intensity continuous-wave laser irradiation. This heating property is an advantage for cancer therapy, when a negatively charged PHF coating on silica NPs functionalized with amine groups was dosed to A549 cells and localized destruction of cells was induced by NIR [159].

Mroz et al. [160] conducted in vivo studies that showed that not only can C_{60} play an important role in cancer therapy on animal models but also that N-methylpyrrolidium-C_{60} (BB4) and white light (more than green light) can have

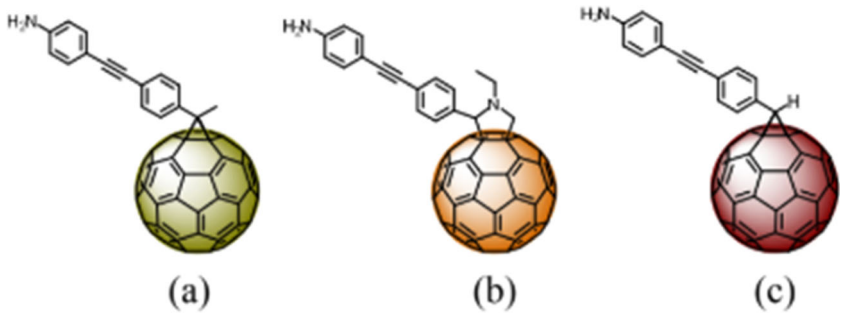

Fig. 8 C_{60} used to physisorbed on the three-dimensional mesoporous graphene macro assemblies electrodes: **a** C_{60}-4, **b** C_{60}-5, **c** C_{60}-7 [152]

significant anticancer benefits in models of disseminated peritoneal carcinomatosis in mice.

In vivo studies have demonstrated the role of C_{60} in PDT. Tabata et al. [158] functionalized C_{60} with PEG and represented C_{60}-based PDT in animal tumors. The study monitored the accumulation and retention times of the C_{60} in the tumors. When exposed to visible light, the C_{60}-PEG conjugate showed more effective tumor suppression than the commercial agent Photofrin. Another study conducted by Tabata et al. [161] described a novel theranostic system based on C_{60}. The group constructed C_{60}-PEG and then conjugated diethylenetridiethylenetriaminepentaacetic acid (DTPA) to the terminal group of PEG to form C_{60}-PEG-DTPA. The C_{60}-PEG-DTPA was then mixed with gadolinium acetate solution to obtain Gd^{3+}-chelated C_{60}-PEG (C_{60}-PEG-Gd). After the C_{60}-PEG-Gd was exposed to light radiation, it caused a decrease in tumor accumulation. This evidence makes the use of C_{60} conjugates a promising approach to cancer theranostics. One of the significant advantages of C_{60} is the response to light irradiation which leads to both generate ROS and $^1O_2$.

In 2012, Lee et al. [162] described that novel functionalized C_{60} could convert light radiation to vibration energy to raise the temperature and generate ROS with light irradiation. In order to enhance the ability of C_{60}, it conjugated with PEG and folate. In vivo PT activity of multimeric C_{60} observed by using cervical carcinoma tumor cells and irradiated with laser light (670 nm) so that they obtained that multimeric C_{60} with folate improved PTT/PDT cell damage.

Shi et al. [163] derivatized ION onto the surface of C_{60} and then applied PEGylation to enhance the solubility and biocompatibility of the complex, obtaining C_{60}-IONP-PEG. Then, they conjugated the complex with the PDT drug hematoporphyrin monomethyl ether (HMME) to demonstrate the conjugated complex's excellent magnetic targeting ability in B16-F10 cells and malignant tumors in mice. In vitro and in vivo studies show that C_{60}-IONP-PEG/HMME released 23-fold DOX and led to strong PDT activity.

Shi et al. [164] improved DOX-loaded polyethyleneimine (PEI) conjugated with C_{60} to form C_{60}-PEI-DOX to enhance the efficiency of chemotherapy and PDT in one system. They loaded DOX onto C_{60} at 490 nm absorption and showed a loading efficiency of 89.2%, indicating that C_{60} is a good DDS. When mice-bearing B16-F10 tumors were treated in vivo with C_{60}-PEI-DOX complexes and a 532-nm laser radiation, the tumor-targeting effect was 2.4 times greater than DOX released in tumor location than normal tissues. In 2014, the same group constructed a hybrid NMs with multifunctional characteristics of PDT and radiofrequency therapy (RFT). The C_{60}-IONP-PEG complex was linked with FA to obtain an active targeting effect in MCF-7 cells and malignant tumors in mice. TUNEL assays were applied to investigate the tumor suppression mechanism of the C_{60}-IONP-PEG/FA complex, and it was found that 62% of cells underwent apoptosis during PDT and 37% of cells underwent apoptosis during RFT. When PDT and RFT were combined, 96% of cells underwent apoptosis.

Combinational therapy is known to provide more effective treatment for cancer and a greater reduction of tumor growth. In 2014, Guo et al. [117] explored the potential advantage of malonic acid fullerene (DMA-C_{60}) in combination with docetaxel (DTX) and micelles (MCs) chemo-PT for tumors. After intravenous injection, it was found that DMA-C_{60} in DTX-MC showed 2.25- and 4.57-fold longer means residence time, the results indicate that DMA-C_{60}/DTX-MC may have significant pharmacokinetic effects. The tumor growth inhibition rate was 81.3%, demonstrating stronger antitumor effects. Additionally, under irradiation DMA-C_{60} improved the cytotoxicity, apoptosis, and antitumor effects of DTX-MC. In another study, microspheres of the hydrophilic antitumor drug mitoxantrone (MTX) were developed with C_{60} 1-phenylalanine derivatives attached with poly-lactic acid (C_{60}-phe-PLA). The treatment was then tested in vivo, and it was found that the relative tumor growth rate was 39.3% after irradiated with a 532-nm laser. This showed that C_{60}-phe-PLA-/MTX can successfully suppress tumor growth and is highly useful for chemotherapy and also in a combination of chemotherapy with PDT [165].

In this review article, we summarize the carbonaceous materials that are used for PT. All materials studied are summarized with respect to their advantages and disadvantages in Table 2.

Table 2 The advantages and disadvantages of GO, CNT and fullerene

Material	Advantages	Disadvantages	Reference
CNTs	Have great potential for drug loading on the internal side of CNTs through the development of nanobottles to carry. It can enter different types of cells via diversified mechanisms using neither energy-dependent nor passive ways of cell uptake.	The lack of solubility in aqueous media. The surface of CNTs must be functionalized with different hydrophilic molecules.	[38, 51, 52, 166]
Carbon dots	Have solubility, good photostability, easy modification, low toxicity and excellent biocompatibility, intense multicolored photoluminescence, and minimal photobleaching.	The high cost of Ca-Ds synthesis	[61]
GO	It illustrates lower toxicity.	Dispersion of GO was not easily achieved in bio-applications due to the binding among GO and proteins/salt in serum.	[95]
C_{60}	Its derivatives generate ROS by illumination.	It is extremely hydrophobic so that it can be aggregate.	[167]
PHFs	Heat and sound waves generation under low-intensity laser irradiation. It is 1.3 nm in size and is able to be easily excreted in the urine.		[158]

7 Future directions of carbon nanomaterial–based phototherapy

As we can summarize, CNs are widely used systems for theranostic applications in cancer treatment. The superior loading capacity, physical properties (intrinsic fluorescence or NIR absorbance), and chemical versatility are the prerequisite for them to be used as potential cancer therapeutics agents [27]. The versatility of CNs allows different DDS, the development of regenerative and stem cell medicine platforms. The increased sensitivity of CNs-based diagnostic devices will contribute to the development of a personalized medical future. Increasing the effectiveness of nanoparticle drug design will also increase the clinical feasibility and implementation of new optimized drug combinations. While this technology has not yet completed the transition to the clinical trial phase, strong preclinical evidence supports promising research for integrated carbon-based nanoscale platforms [38]. The improvement of different engineered NIR light–absorbing NMs will continue to attract interest in the topic of cancer therapy and beyond [7].

8 Conclusion

PT offers advantages over conventional treatment methods such as radio and chemotherapy. It provides safety; minimal invasion; and high selectivity, it is cost-effective and suppresses extensive utilization of peripheral lesions [168]. In this review, we consistently reviewed the recent benefits in PT of cancer using CNs such as graphene, GO, CNTs, and C_{60}. These CNs exhibit a critical role in cancer therapy. The surface chemistry of NMs provides high interactions of chemicals and biomolecules at the interface section, and it will play an important role in applying graphene; CNTs; and C_{60} as either chemical or biosensing, DDS and imaging in PT [32].

Diverse strategies were developed as to NMs with respect to PS carrier systems containing targeted, target-activatable, PTT, and PDT neither in vitro nor in vivo. Suitable, well-designed CNs fulfill clinical requirements. Current challenges include the development of versatile graphene, CNTs or C_{60}-based nanocarriers for medical diagnosis and therapy. Moreover, suitable modification and functionalization on NMs can improve their biocompatibility, solubility, drug loading capability, and delivery efficiency. Cellular uptake mechanisms and intracellular metabolic pathways of NMs are still unknown although they are crucial for in vivo research. However, this work provides venues for future scientific research developments. In addition, the advantages offered by these NMs in cancer therapies remain indisputable. Based on previous studies, the exceptional nature and the high potential of graphene, CNTs and C_{60} in PTs are highlighted. Future research could be based on functionalization strategies for precise drug delivery and treatment. CNs have the capacity to detect and respond to dynamic changes of proteins, nucleic acids either DNA or RNA. Additionally, functional NMs play significant roles for cancer treatment based on PTT, mainly because of their unique properties, and minimal side effects and high efficiency.

Acknowledgements This work was funded by Yıldız Technical University under the contract number 2016-07-04-YL10.

Compliance with ethical standards

Competing interests The authors declare that they have no conflict of interest.

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